Lack of association of biologic therapy for psoriasis with psychiatric illness: An electronic medical records cohort study

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Background: Psoriasis and biologic therapies have been associated with psychiatric illnesses.

Objective: To determine if persons with psoriasis or those exposed to biologics are more likely to develop a psychiatric illness.

Methods: Retrospective electronic medical records cohort study.

Results: Individuals with psoriasis were significantly more likely to have a history of several medical (eg, cardiovascular illnesses) and psychiatric (eg, depression, suicide) illnesses than those without psoriasis. Those with psoriasis who were prescribed a biologic therapy were significantly less likely than those with psoriasis not prescribed a biologic agent to receive a psychiatric illness diagnosis (hazard ratio for any psychiatric illness 0.52, 95% confidence interval 0.51-0.53, $P < .0001$). With respect to any psychiatric illness, this finding was confirmed when comparing biologic therapy versus methotrexate treatment (0.80, 95% confidence interval 0.76-0.84, $P < .0001$).

Limitations: These findings were likely attributable to treatment selection bias.

Conclusion: Individuals with psoriasis have an increased risk of several medical and psychiatric illnesses. Individuals with psoriasis prescribed biologic agents are less likely than those not prescribed biologic agents to develop psychiatric illnesses. Most likely because of treatment selection, individuals with psoriasis prescribed biologic therapy are not currently at increased risk of a psychiatric outcome. (J Am Acad Dermatol 2019;81:709-16.)

Key words: biologic therapy; bipolar disease; depression; psoriasis; psychiatric illness; suicide.

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Psoriasis is a common inflammatory disease that affects 1%-3% of the general population, that is, ~7.5 million adults in the United States.[1,2] About 20% of those with psoriasis will have moderate-to-severe psoriasis and are potentially a candidate for systemic therapy. Systemic treatment of moderate-to-severe psoriasis was revolutionized by the advent of biologic agents.[3] The safety profile of these agents as a group has been excellent; however, because of their ability to modulate immune function, the Food and Drug Administration (FDA) has had concerns about potential short- and long-term adverse events.

A recent meta-analysis reported that patients with psoriasis are 1.5 times more likely to experience depression than healthy controls (odds ratio 1.57, 95% confidence interval [CI] 1.40-1.76).[4] Compared with other dermatologic diseases, such as acne or atopic dermatitis, individuals with psoriasis have higher rates of mental health outcomes.[5] Social factors, such as stigmatization and self-stigmatization of persons with psoriasis, can contribute to psychiatric outcomes.[6,7] In addition, the inflammatory mediators associated with psoriasis are also postulated to be associated with the development of the psychiatric comorbidities seen in patients with psoriasis.[8]

In general, improvement of cutaneous psoriasis is associated with improvement in psychologic symptoms, such as depression, in clinical trials.[9] However, a variety of psoriasis treatments of varying mechanisms of action, such as retinoids (acitretin), interleukin 17 receptor blockade (brodalumab), and phosphodiesterase 4 inhibition (apremilast), have warnings on their FDA labels detailing the risk of mental health outcomes (eg, self-harm or suicidality).[9,10] In addition, other biologic mechanisms of action, such as tumor necrosis factor inhibition, have been associated with serious mental health outcomes in sporadic case reports.[11]

The primary objective of this study was to determine if those with psoriasis prescribed a biologic therapy were more likely than those not prescribed a biologic to have a psychiatric illness develop by using a large, US electronic medical records database. To explore this question, we compared the rates and likelihoods of mental health disease (overall psychiatric disease, depression, psychosis, bipolar disorder, suicide, or suicidal ideation) between patients with and without psoriasis, patients with psoriasis prescribed and not prescribed a biologic agent, and patients with psoriasis prescribed a biologic agent versus methotrexate.

CAPSULE SUMMARY

- Psoriasis and treatments for psoriasis have been associated with several serious psychiatric illnesses.
- The prescription of biologic therapies to treat psoriasis does not appear to be associated with psychiatric illnesses. The lack of an association is likely due to the prescribing behaviors of physicians (selection bias), who appear to be mediating these potential adverse psychiatric events by carefully selecting the patients receiving the treatment.

METHODS

The population

OptumInsights Electronic Health Record (OEHR) database (previously Humedica), contains deidentified patient-level data on 81 million individuals and their health care encounters, making OEHR the largest electronic health record source in the United States.[12] About 70% of individuals whose data are included in OEHR are from integrated delivery networks, meaning that all of a patient's health care encounters within the network are captured in the OEHR database.[13] OEHR includes health care networks from 38 states within the United States.[12-14] We evaluated 2 data sets (a 10% random sample of the complete OEHR data set and every individual with psoriasis in the complete OEHR data set) for the health care encounters that took place during January 1, 2007-June 30, 2017. The University of Pennsylvania Institutional Review Board approved it as an exempted category 4 study (protocol # 827734).

Psoriasis

The diagnosis of psoriasis, excluding individuals with psoriatic arthritis, was based on the use of International Classification of Diseases, Ninth Revision (ICD-9), or Tenth Revision (ICD-10), codes at 2 distinct patient encounters. This diagnostic algorithm we used was previously validated to identify individuals with psoriasis from administrative or medical record databases.[15,16] Because the biologic therapies evaluated in this study were approved for the treatment of psoriasis and insurance approval to receive these agents is highly regulated, an exception was made to the algorithm on biologic therapy prescription. In this setting, a single ICD-9 or ICD-10 code consistent with psoriasis and a prescription for any biologic therapy, methotrexate, or phototherapy confirmed the psoriasis diagnosis. After the second event, the

Abbreviations used:

CI:	confidence interval
FDA:	Food and Drug Administration
HR:	hazard ratio
ICD-9:	International Classification of Diseases, Ninth Revision
ICD-10:	International Classification of Diseases, Tenth Revision
IQR:	interquartile range
OEHR:	OptumInsights Electronic Health Record
SD:	standard deviation

individual qualified for the study and began to accrue follow-up time. A similar algorithm was used to assure that those without psoriasis were active in the health care system. Individuals without a history of psoriasis were evaluated if they had 2 separate patient visits.

Drug exposure

The biologic agents evaluated were adalimumab, etanercept, ustekinumab, ixekizumab, and secukinumab. A composite was created for all of these biologics, as well as for interleukin 17 inhibitors (ixekizumab and secukinumab) and subcutaneous tumor necrosis factor inhibitors (adalimumab and etanercept). In addition, apremilast and methotrexate were evaluated. To control for potential confounding by disease severity, methotrexate (like biologics used to treat moderate-to-severe psoriasis) was evaluated as a comparison agent. Because of the time period of the data available for study and FDA approval dates, brodalumab was not studied (no users).

Outcome and covariates

The outcomes of interest for this study were any psychiatric illness, depression, psychosis, bipolar disease, suicide, or suicidal ideation. All of these outcomes were determined by ICD-9 or ICD-10 codes and, if indicated, appropriate injury codes (available at: https://doi.org/10.17632/7994cjkfwr.1). In addition, we evaluated basic sociodemographic factors (such as age, sex, race, and geographic location), income, percentage with college education by 3-digit zip code, and comorbid illnesses (such as congestive heart failure, chronic renal disease, chronic obstructive pulmonary disease, cerebrovascular accident, diabetes, hypertension, and myocardial infarction).

Analysis

Separate analyses were performed with the OEHR 10% random sample and OEHR complete psoriasis cohort. Descriptive analyses were described by using the mean and standard deviation (SD) or the median and interquartile range (IQR), as appropriate. Associations were determined by using logistic regression or proportional hazards models. Adjusted models included the sociodemographic factors previously listed. The start date for all individuals was the second qualifying action. All patients were censored at the time of an outcome, death, or at their last health care encounter. The proportional hazards assumptions were met by all proportional hazards models. Our primary question was whether prescription for biologic therapies increased the risk of psychiatric illness in adults with psoriasis; once an agent was prescribed, an individual accrued time related to that agent until the end of observation.

RESULTS

The OEHR 10% data set contained information from 5,858,998 individuals followed for 25,885,998 total person-years. Using the algorithm described, we identified 26,208 (0.44%) patients with psoriasis. The total follow-up for the psoriasis cohort was 71,528 person-years, and the total follow-up for those without a diagnosis of psoriasis was 25,688,526 person-years. The average follow-up time was 4.40 (SD 3.54) years, and the median was 3.74 (IQR 1.08-7.16) years. For those without psoriasis, the average follow-up time was 4.40 (SD 3.55) years, and the median was 3.74 (IQR 1.08-7.24) years. For those with psoriasis, the average follow-up time was 2.73 (SD 2.22) years, and the median was 2.32 (IQR 0.92-4.06) years. The average age at entry into the 10% OEHR cohort was 38.44 (SD 23.39) years, and the median was 38.67 (IQR 19.92-56.59) years; 55.20% were female. The average age at entry for those without psoriasis was 38.38 (SD 23.40) years, and the median was 38.59 (IQR 19.83-56.50) years; 55.21% were female. For those with psoriasis, the average age at entry was 51.48 (SD 17.53) years, and the median was 52.94 (IQR 39.32-64.00) years; 52.99% were female. In total, 12.77% of those with psoriasis and 0.21% of those without psoriasis were prescribed a biologic agent.

Table I presents comparisons of the frequencies of demographic and health-related factors with onset after the official psoriasis (for the psoriasis cohort) or no psoriasis diagnosis (for the control cohort). Those with psoriasis were more likely to be male, older, white, from the Northeast region, and from areas with higher rates of college education. Although these differences are statistically significant, the magnitude of these differences was small, with the exception of age and race. Table II shows the rate of diagnosis per 1000 person-years for important medical and psychiatric illness, which were all more common in those with psoriasis.

Table I. Demographic factors of the entire 10% random sample and the psoriasis and nonpsoriasis cohorts within the 10% sample of the OEHR data set

Characteristic	Entire 10% sample, N = 5,858,998	Nonpsoriasis cohort, n = 5,832,790	Psoriasis cohort, n = 26,208	Unadjusted OR (95% CI)	Fully adjusted selective OR (95% CI)*
Sex, female, %	55.20	55.21	52.99	0.91 (0.89-0.94)†	0.90 (0.88-0.92)†
Age, y, mean (SD)	38.44 (23.39)	38.38 (23.40)	51.48 (17.53)	1.02 (1.02-1.02)†	1.02 (1.02-1.02)†
Race/ethnicity, %					
Black	9.44	9.47	3.64	Reference	Reference
Asian	2.19	2.19	2.05	2.43 (2.19-2.70)†	2.29 (2.06-2.26)†
White	65.88	65.80	82.93	3.27 (3.07-3.49)†	3.20 (3.00-3.43)†
Unknown/other	22.49	22.54	11.38	1.31 (1.22-1.41)†	1.27 (1.18-1.37)†
Region, %					
Midwest	41.65	41.65	43.74	Reference	Reference
Northeast	11.58	11.57	14.88	1.22 (1.18-1.27)†	1.26 (1.21-1.31)†
Unknown, other	5.07	5.08	3.31	0.62 (0.58-0.66)†	1.64 (0.41-6.60)
South	29.44	29.46	26.37	0.85 (0.83-0.88)†	0.91 (0.88-0.94)†
West	12.25	12.25	11.71	0.91 (0.87-0.95)†	1.00 (0.96-1.04)
Income,‡ USD, average (SD)	43,216 (10,443.1)	43,215 (10,441.38)	43,877 (10,793.59)	1.00 (1.00-1.00)†	1.00 (1.00-1.00)
College education,‡ %	24.79	24.79	25.02	1.00 (1.00-1.01)†	1.01 (1.00-0.02)†

CI, Confidence interval; *OEHR*, OptumInsights Electronic Health Record; *OR*, odds ratio; *SD*, standard deviation; *USD*, US dollar.
*Adjusted for sex, race, geographic location, income, and percentage with college education.
†$P < .001$.
‡Based on 3-digit zip code aggregate data.

Table II. Medical or psychiatric outcomes of interest in entire 10% random sample and psoriasis and nonpsoriasis cohorts within the 10% sample of the OEHR data set

Outcome	Rate, event/1000 (95% CI) person-years			Unadjusted HR (95% CI)	Fully adjusted HR (95% CI)
	Entire 10% sample, N = 5,858,998	Nonpsoriasis cohort, n = 5,832,790	Psoriasis cohort, n = 26,208		
Congestive heart failure	7.00 (6.97-7.04)	6.96 (9.93-6.99)	22.73 (21.63-23.89)	3.41 (3.24-3.58)	3.33 (3.16-3.50)
Chronic kidney disease	8.31 (8.27-8.34)	8.25 (8.21-8.28)	31.53 (30.21-32.90)	4.15 (3.98-4.33)	4.14 (3.96-4.32)
Chronic obstructive pulmonary disease	9.11 (9.08-9.15)	9.04 (9.00-9.08)	37.57 (36.11-39.09)	4.29 (4.11-4.45)	4.09 (3.93-4.26)
Cerebrovascular accident	8.18 (8.14-8.21)	8.13 (8.09-8.06)	25.84 (25.64-27.09)	3.35 (3.19-3.51)	3.20 (3.06-3.36)
Diabetes	19.48 (19.42-19.53)	19.33 (19.28-19.39)	79.08 (76.83-81.39)	3.73 (3.63-3.84)	3.80 (3.69-3.92)
Hypertension	52.70 (52.60-52.79)	52.31 (52.22-52.41)	253.95 (249.16-258.83)	4.50 (4.42-4.59)	4.48 (4.39-4.56)
Any psychiatric illness	40.57 (40.48-40.65)	40.31 (40.23-40.40)	157.34 (153.89-160.89)	4.13 (4.04-4.22)	4.04 (3.94-4.13)
Suicide	0.57 (0.56-0.58)	0.57 (0.56-0.58)	1.02 (0.81-1.29)	2.05 (1.63-2.58)	Did not converge
Suicidal ideation	0.79 (0.75-0.80)	0.78 (0.77-0.79)	1.84 (1.55-2.18)	3.42 (2.88-4.07)	Did not converge
Depression	26.54 (26.48-26.61)	26.37 (26.30-26.44)	100.72 (98.10-103.40)	4.07 (3.96-4.18)	3.98 (3.88-4.09)
Psychosis	4.17 (4.15-4.20)	4.16 (4.13-4.18)	10.85 (10.10-11.66)	2.86 (2.67-3.08)	2.84 (2.64-3.06)
Bipolar	2.96 (2.94-2.99)	2.95 (2.93-2.97)	8.83 (8.16-9.56)	3.01 (2.78-3.26)	3.00 (2.76-3.25)

For all HRs, $P < .0001$.
CI, Confidence interval; *HR*, hazard ratio; *OEHR*, OptumInsights Electronic Health Record.

Within the complete OEHR database, 262,552 patients were identified as having psoriasis. Women comprised 52.91% of this cohort, and 83.10% were white (Table III). The mean age of patients at a qualifying diagnosis was 51.23 (SD 17.61) years, and the median age was 53.15 (IQR

Table III. Demographic factors of the complete psoriasis cohort and of psoriasis patients prescribed and not prescribed biologics from the complete OEHR data set

Characteristic	Complete psoriasis cohort, n = 262,552	No biologic prescription, n = 228,830	Biologic prescription, n = 33,722	Fully adjusted OR* (95% CI) for biologic use
Sex, female, %	52.97	53.18	51.55	1.10 (1.08-1.13)†
Age, y, mean (SD)	51.53 (17.61)	52.09 (18.00)	47.72 (14.13)	0.99 (0.99-0.99)†
Race/ethnicity, %				
Black	3.55	3.64	2.94	Reference
Asian	2.14	2.14	2.15	1.27 (1.14-1.40)†
White	83.14	82.93	84.56	1.24 (1.15-1.32)†
Unknown/other	11.16	11.28	10.35	1.11 (1.02-1.20)†
Region, %				
Midwest	44.18	44.36	42.94	Reference
Northeast	14.39	14.11	16.28	1.24 (1.20-1.29)†
Unknown, other	3.30	3.36	2.88	0.89 (0.11-7.14)
South	26.54	26.42	27.32	1.08 (1.05-1.11)†
West	11.59	11.74	10.58	0.97 (0.93-1.01)
Income,‡ USD, average (SD)	43,907 (10,718)	43,987 (10,679)	43,907 (10,978)	1.00 (1.00-1.00)
College education,‡ %	25.01	25.04	24.78	0.99 (0.99-0.99)†

CI, Confidence interval; *OEHR*, OptumInsights Electronic Health Record; *OR*, odds ratio; *SD*, standard deviation; *USD*, US dollar.
*Adjusted for sex, race, geographic location, income, and percentage with college education.
†$P < .001$.
‡Based on 3-digit zip code aggregate data.

Table IV. Disease history of complete psoriasis cohort and psoriasis patients prescribed and not prescribed biologics from the complete OEHR data set

Outcome	Complete psoriasis cohort, n = 262,552, %	No biologic prescription, n = 228,830, %	Biologic prescription, n = 33,722, %	Fully adjusted OR (95% CI) for biologic use
Congestive heart failure	7.12	7.87	1.96*	0.75 (0.52-0.63)*
Any psychiatric illness	37.18	38.90	25.47	0.67 (0.65-0.68)
Chronic kidney disease	9.42	10.32	3.33*	0.70 (0.64-0.75)*
Chronic obstructive pulmonary disease	11.01	11.99	4.35*	0.60 (0.56-0.64)*
Cerebrovascular accident	8.59	9.41	3.03*	0.58 (0.53-0.62)*
Diabetes	20.08	20.98	13.94*	1.01 (0.97-1.04)
Hypertension	46.03	48.17	31.44*	0.71 (0.69-0.73)*

History was based on database coding for the illness of interest before confirmation of the psoriasis diagnosis or before the prescription code for a biologic treatment. Initial associations were compared by using the chi squared test. The time of observation until patients qualified for inclusion in the psoriasis cohort (ie, met inclusion criteria for a psoriasis diagnosis or received a prescription for a biologic) was on average 4.38 (SD 3.07) years for the full cohort, 4.39 (SD 3.06) years for those who did not receive a prescription for a biologic, and 4.31 (SD 3.14)* years for those who received a prescription for a biologic.
CI, Confidence interval; *OEHR*, OptumInsights Electronic Health Record; *OR*, odds ratio; *SD*, standard deviation.
*$P < .0001$.

39.41-64.16) years. This data set contains ~697,625 person-years of follow-up; the mean time of follow-up per person in this cohort was 2.75 (SD 2.22) years, and the median time was 2.31 (IQR 0.89-4.05) years. The mean follow-up time for those who did not receive a prescription for a biologic was 2.62 (SD 2.15) years and for those who did was 3.58 (SD 2.48) years. Those prescribed a biologic were younger, more likely to be white, and less likely to have a history of any of the medical illnesses of interest (Table IV). Those prescribed biologics were less likely than those prescribed methotrexate to have a history of myocardial infarction, cerebrovascular accident, or chronic obstructive pulmonary disease, and those prescribed methotrexate were less likely to have chronic kidney disease and any psychiatric illness than those prescribed a biologic.

The rates of psychiatric illness onset after a qualifying psoriasis diagnosis or first prescription of biologics per 1000 person-years is presented in

Table V. Comparison of rates of psychiatric outcomes between psoriasis patients prescribed and not prescribed biologics or prescribed methotrexate from the complete OEHR data set

	Rate, event/1000 (95% CI) person-years				Rate, event/1000 (95% CI) person-years			
Outcome	No biologic prescription, n = 228,830	Biologic prescription, n = 33,722	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Methotrexate prescription, n = 15,133	Biologic prescription,* n = 22,592	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Suicide	0.95 (0.88-1.04), n = 217	0.51 (0.40-0.65), n = 17	0.57 (0.44-0.75)†	0.52 (0.40-0.69)†	0.48 (0.32-0.72), n = 7	0.56 (0.42-0.76), n = 13	1.17 (0.71-1.95)	1.16 (0.67-2.01)
Suicidal ideation	1.88 (1.77-1.99), n = 430	1.11 (0.94-1.32), n = 37	0.59 (0.49-0.71)†	0.57 (0.48-0.69)†	0.96 (0.72-1.28), n = 14	1.21 (0.99-1.49), n = 27	1.26 (0.89-1.80)	1.18 (0.81-1.70)
Depression	103.71 (102.78-104.65), n = 23,732	51.71 (50.28-53.18), n = 1744	0.56 (0.54-0.58)	0.58 (0.57-0.60)†	64.60 (62.04-67.26), n = 978	51.00 (49.22-52.84), n = 1152	0.80 (0.76-0.85)†	0.93 (0.88-0.99)
Psychosis	11.24 (10.96-11.51), n = 2572	4.13 (3.78-4.52), n = 139	0.40 (0.37-0.44)†	0.45 (0.41-0.49)†	6.47 (5.78-7.25), n = 98	4.19 (3.74-4.68), n = 95	0.65 (0.55-0.76)†	0.77 (0.65-0.91)†
All psychiatric illnesses	165.50 (164.26-166.75), n = 38,871	73.77 (71.98-75.60), n = 2488	0.50 (0.49-0.52)†	0.52 (0.51-0.53)†	97.34 (94.04-100.76), n = 1718	76.05 (73.79-78.39), n = 1718	0.80 (0.76-0.84)†	0.91 (0.87-0.96)†
Bipolar illness	8.79 (8.55-9.03), n = 2011	4.15 (3.80-4.54), n = 140	0.55 (0.50-0.60)†	0.53 (0.48-0.58)†	4.75 (4.17-5.42), n = 95	4.22 (3.78-4.72), n = 95	0.90 (0.76-1.07)	0.91 (0.76-1.09)

Supplemental Tables (available at: https://doi.org/10.17632/7994cjkfwr.1) present comparisons between individual biologics (adalimumab, etanercept, ustekinumab, ixekizumab, secukinumab, and apremilast) and methotrexate and tumor necrosis factor and interleukin 17 agents as composites.

CI, Confidence interval; *HR*, hazard ratio; *OEHR*, OptumInsights Electronic Health Record.

*Total number of individuals prescribed biologics in this listing is smaller than the number in the previous listing because individuals included in this listing could only be prescribed methotrexate or a biologic and but not both.

†All HR *P* values <.0001.

Table V. Individuals prescribed >1 agent were excluded from this analysis. Table V shows comparisons between psoriasis patients prescribed a biologic and those without a prescription for a biologic or with a prescription for methotrexate, as well as the rates of psychiatric events. Patients prescribed a biologic were, in general, less likely to have a documented psychiatric illness of interest than those with psoriasis not prescribed a biologic and, specifically, when compared with those prescribed methotrexate. Similar findings were noted for each biologic agent versus methotrexate (data not shown; available at: https://doi.org/10.17632/7994cjkfwr.1). Average follow-up time was similar among the biologic and methotrexate comparison groups and ranged ~2.3-2.8 years.

DISCUSSION

To the best of our knowledge, our study including a single US-based electronic medical records data set is the largest study of individuals with psoriasis. First, we studied a 10% random sample of the full OEHR data set that contained information from ~6 million people followed for ~26 million total person-years. About 0.44% of those in the data set had psoriasis, of whom 12.77% were prescribed a biologic agent. As previously described, those with psoriasis were more likely to have a history of several chronic medical illnesses. Furthermore, those with psoriasis were more likely than those without psoriasis to have a diagnosis of any psychiatric illness, depression, bipolar disease, psychosis, suicide, and suicidal ideation. Many of these findings are consistent with previous studies.[9,17,18] We also made use of a second cohort consisting of >250,000 psoriasis patients with almost 700,000 person-years of follow-up. The main purpose of this cohort was to enhance our understanding of the relationship between the biologic medication prescription and psychiatric illnesses in those with psoriasis. Surprisingly, those prescribed a biologic seemed healthier than those not prescribed a biologic in that they were less likely at their qualifying date to have a history of psychiatric illness, congestive heart failure, chronic kidney disease, myocardial infarction, cerebrovascular accident, diabetes, hypertension, or chronic obstructive pulmonary disease. In addition, those prescribed biologics were less likely than those not prescribed biologics to develop any psychiatric illness, depression, bipolar disease, psychosis, suicide, or suicidal ideation.

We next compared biologics with methotrexate, which is another therapy used for the treatment of moderate-to-severe psoriasis. With the exception of suicidal ideation and suicide, those prescribed any biologic or a specific biologic agent were generally and consistently less likely than those prescribed methotrexate to have a psychiatric illness diagnosis. With respect to suicidal ideation and suicide, there was no difference between therapies. Although it is possible that biologics have a preventative effect on psychiatric illness because there was a decreased likelihood for a multitude of medical illness among those who were prescribed a biologic, it is more likely that those who were selected to receive a biologic were different and perhaps healthier than those not prescribed a biologic.

A recent meta-analysis from Singh et al of 18 studies and 330,207 people with psoriasis showed that those with psoriasis were more likely to exhibit suicidal ideation (pooled OR 2.05, 95% CI 1.54-2.74).[19] The studies analyzed were primarily case-control and cohort studies.[19] In our study of the OEHR 10%, we noted a similar hazard ratio (HR) to Singh et al for those with psoriasis compared those without (3.42, 95% CI 2.88-4.07) and a rate of 1.84 cases/1000 person-years.[19] Depression and anxiety were noted in 14.7% of the Psoriasis Longitudinal Assessment and Registry patients; depression was noted in ~10.1% and any psychiatric illness in ~15.7% of the 10% OEHR sample cohort, with similar estimates in the complete psoriasis OEHR cohort.[20] In a study of data from children from a US administrative database, researchers noted an HR of 1.23 (95% CI 1.06-1.43) for the onset of depression among children with psoriasis compared with those without a diagnosis of psoriasis.[18] Kurd et al using a UK patient record database noted similar findings.[17] In their study, an HR of 1.39 (95% CI 1.37-1.41) was noted for depression and 1.44 (95% CI 1.32-1.57) for suicidality. In our study, the HR was much larger for depression (4.07, 95% CI 3.96-4.18) and suicidal ideation (3.42, 95% CI 2.88-4.07).[17] Interestingly, a recent study by Parisi et al using a similar UK data set as used by Kurd et al did not find an increased risk of completed suicide, although there was an increased risk of self-harm (HR 1.15, 95% CI 1.04-1.27).[21]

Our study is a cohort study and therefore carries with it some limitations. Treatment selection can have an influence on the results of this and any study. In fact, selection bias is likely the reason that those prescribed biologics were less likely to develop psychiatric illness in this study. Forms of information bias could also have affected this study. Although the OEHR data set is large with data from 38 states and the majority of the medical systems that contribute information are integrated medical systems, most of the medical systems are not closed. As a result, patients could seek health care with providers who were not part of the OEHR data collection network, and the outcomes of these visits would likely not

have been available for analysis. We used validated outcomes when possible. However, it seems unlikely, for example, that those prescribed methotrexate would be less likely than those prescribed biologics to seek care outside of database providers or that the determination of outcome would vary by drug exposure. Furthermore, medication use was based on providers writing prescriptions; it was not known if the patient received the medication. Because of insurance restrictions, it is possible that actual medication use after prescription might have varied by agent.

When using a large national electronic medical records database, individuals with psoriasis had an increased risk of several cardiovascular diseases and psychiatric illnesses. Individuals with psoriasis prescribed biologic agents were less likely to have a history of cardiovascular disease and psychiatric illnesses than those not prescribed biologic agents. Those prescribed biologic agents were also less likely to later receive psychiatric illness diagnoses and less likely to manifest suicidal behaviors. Although it is possible that biologic therapy had a direct influence on the development of psychiatric illnesses in our study, biologic treatment selection favoring healthier individuals with psoriasis is likely associated with our failure to find an increased risk of a psychiatric outcomes. It might even be possible that physicians are selecting patients to receive a biologic agent to minimize adverse events. Further investigations are required to better elucidate these outcomes.

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